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INCREASED BRAIN RADIORESISTANCE AFTER SUPRALETHAL IRRADIATION

R. L. Chaput
P. A. Berardo
with the technical assistance of
E. L. Barron

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

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Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

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R. L. CHAPUT
P. A. BERARDO
with the technical assistance of
E. L. BARRON

JOE E. WEST
Lieutenant Colonel, USAF, VC
Chairman
Radiation Biology Department

R. E. CARTER
Chairman
Physical Sciences Department

MYRON I. VARON
Captain MC USN
Director

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

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FOREWORD
(Nontechnical summary)

Previous experiments with miniature pigs have shown that performance was significantly better after a supralethal dose of radiation when it was in two equal fractions than when unfractionated. Further, clinical symptoms were less severe and performance was generally better after the second than after the first dose fraction. This increased radioresistance to the second dose was evident when the time interval between doses was varied from 1/2 to 24 hours.

This study was designed to investigate the time dependence of the increased radioresistance and thereby gain some understanding of the mechanisms involved. Performance was evaluated after shuttlebox-trained miniature pigs received two 4400-rad doses separated by time intervals of 10^{-4} to 30 minutes. The minimum time interval between dose fractions of 10^{-4} minute was considered an unfractionated or control dose. The doses were delivered to the head by high energy electrons from the AFRRI electron linear accelerator (LINAC).

There was no significant difference in performance after the second dose fraction between animals that received the two doses 10^{-4} or 0.3 minute apart. As the time interval between dose fractions was increased from 0.3 to 3 minutes, performance after the second dose fraction improved markedly. When the doses were 30 minutes apart, the pigs showed no early performance decrement after the second dose of radiation.

ABSTRACT

Clinical symptoms and performance were evaluated after shuttlebox-trained miniature pigs received two 4400-rad doses separated by time intervals of 10^{-4} to 30 minutes. The doses were delivered to the head by 45 MeV electrons from the AFRRI electron linear accelerator (LINAC). There was no significant difference in neurological symptoms (convulsions, coma, ataxia) or in performance after the second dose between animals that received the two doses 10^{-4} or 0.3 minute apart. As the time interval between doses was increased from 0.3 to 3 minutes, however, neurological symptoms declined and performance improved markedly after the second dose. When the doses were 30 minutes apart, the pigs showed no decrease in performance within the initial 30 minutes postirradiation. It was concluded that more than physicochemical processes were involved in the increased radioresistance to the second dose of radiation.

I. INTRODUCTION

Previous studies have shown that various animal species can recover to a relatively large extent from sublethal radiation injury.[1,11,14,15] Only recently has it been demonstrated that an apparent recovery phenomenon also occurs after lethal[3,4] and supralethal whole-body doses of radiation.[2,6,7,9,13,21,22]

In addition to increased survival time, miniature pig performance following a whole-body fractionated supralethal dose was significantly better than after a similar unfractionated dose.[7] Furthermore, neurological symptoms (convulsions, coma, ataxia) and performance decrement usually observed within the first 30 minutes postirradiation were generally less severe after the second than after the first dose. Similar results have been observed for the rat[6] and rhesus monkey[9,13,21] after whole-body fractionated doses of radiation.

A reduced response to the second dose of radiation was clearly manifested within 30 minutes postirradiation.[6,7] The mechanisms responsible for this effect are not known. They could be solely physicochemical, biochemical, or physiological, or a dynamic combination of these. Clearly, physicochemical processes would require only a fraction of a second, whereas biochemical and physiological processes would require seconds to minutes to become effective. By investigating the time dependence of the increased radioresistance, some understanding of these mechanisms could be gained. Thus, in this study, miniature pigs received two 4400-rad doses separated by time intervals of 10^{-4} to 30 minutes. Clinical symptoms and shuttlebox performance were evaluated.

Earlier work has shown that radiation effects upon head structures were the primary cause of neurological symptoms and rapid death in miniature pigs.[18] Therefore, in this study the dose was restricted to the animal's brain.

II. PROCEDURES

Experimental animals. The animals were 40 miniature pigs (male, female, and barrow) of the Hormel strain. They were young adults, 4 to 6 months old, and weighed 20 to 40 kg when irradiated.

All pigs were trained by shock avoidance conditioning to cross a two-chambered shuttlebox, as previously described.[7] During each trial the pig had 6 seconds to avoid electrical shock by crossing the shuttlebox while visual and auditory cues were presented, 4 seconds to escape electrical shock by crossing after shock was initiated, and 3 seconds to rest. A failure was scored when the animal did not cross the box in a given trial. For purposes of this study, failures and escapes were considered as omissions. Before irradiation, each pig was trained to a minimum performance criterion of 90 percent avoidance.

Radiation source. In earlier investigations,[6,7] the animals received whole-body mixed gamma-neutron radiation from fission reactors. Instead of a reactor, the AFRRI electron linear accelerator (LINAC) was used as the radiation source because it is capable of providing head-only irradiation without shielding, better depth-dose distribution, and shorter time intervals between dose fractions.

Dosimetry. The influence of the magnitude of the initial dose on recovery was not examined in this study. However, previous work has demonstrated that the first

dose of radiation must exceed approximately 4000 rads for the pig[7] and 2500 rads for the monkey[13] for increased radioresistance to a second supralethal dose. Thus, an initial dose of 4400 rads was used to ensure that a measurable radioresistant state was produced in the pigs. The pigs were given two 4400-rad doses to the brain, separated in time by 10^{-4}, 0.3, 1.6, 3.0 or 30 minutes.

Inasmuch as the LINAC irradiations were a continuation of an experimental program started with the reactor, an attempt was made to duplicate the irradiation time. With the reactor, a dose of 8800 rads was delivered in a single pulse of about 15 msec. Table I lists some of the irradiation parameters used for the various experiments in this study. With the LINAC, the minimum time interval between dose fractions was $\approx 10^{-4}$ minute ($\approx$8 msec between pulses) and was considered an unfractionated or single dose. The single dose experiments with the LINAC were carried out to compare the relative effectiveness on performance between electrons and the mixed gamma-neutron field of the reactor. The change in energy from 43 to 45 MeV was to slightly improve the depth-dose distribution. Fractionated dose experiments were conducted using two series, with 8 pigs in the first and 32 pigs in the second.

	Single dose	Fractionated dose	
		Series 1	Series 2
Energy, MeV	43	45	45
Pulse width, μsec	4.1	4.0	4.0
Pulse frequency, Hz	120	120	120
Current, mA	500	405	315
Pulses/fraction	5	4	5
Dose/pulse, rads	1735	1100	882
Dose/fraction, rads	8675	4400	4410

Table I. Irradiation Parameters

Absorbed doses were measured with thermoluminescent dosimeters (Harshaw TLD-700) and a reader (Harshaw Chemical Company Model 2000). The TLD's and reader were calibrated with AFRRI's ^{60}Co facility against a 3-cm^3 ion chamber calibrated at the National Bureau of Standards. Unless otherwise indicated, doses are midbrain and are accurate to ±5 percent.

The change in beam current between series 1 and series 2 is reflected by different dose rates for each series. However, the total delivery time for 4400 rads was only changed from 33 to 25 msec. This corresponds to an average dose rate of 132 and 176 krads/sec, respectively. The corresponding instantaneous dose rates (dose rate during a pulse) were 220 and 275 Mrads/sec, respectively. In both cases, dose delivery times were negligible relative to the time intervals for performance evaluation.

Dose distributions. The objectives were to achieve a class A dose distribution in the brain (the dose at all points in the brain to be at least 87 percent of maximum) and to minimize the dose to the body. The field shape and center were measured with diodes behind the front Plexiglas plate of the animal restraint cage. A typical beam profile is shown in Figure 1. The class A field diameter was 6 cm, which easily included the typical 5-cm diameter of the pig brain.

To determine the dose distribution within the head, a pig-head phantom containing TLD's was irradiated. The phantom consisted of a skull imbedded in paraffin. Lucite rods, each containing a TLD, were inserted into eight holes drilled vertically from the dorsal surface into the phantom. The placement of the TLD's was verified by inserting small metal rods into the holes and x raying the phantom. The relative

doses are shown in Figure 2 and conform to a class A dose distribution within the brain. The rapid decrease in dose, with displacement from the beam center line, allowed the experiment to be conducted without shielding material for the body. Measurements in a pig cadaver showed that, relative to the midbrain dose, the doses in the middle of the neck and trunk were about 23 percent, and less than 1 percent, respectively.

Alignment. During irradiation, each pig was restrained in a Plexiglas box and positioned with its left side toward and 3.5 meters from the beam port. The small field size required that the pig's head be carefully aligned with the beam. The cage constrained the animal so that it would consistently place its snout in a breathing port. Thus, the position of the brain relative to the cage was essentially fixed. A target was placed on the cage to indicate where the beam should enter for the brain irradiations. Before each irradiation, the target was aligned with the peak of the beam profile (Figure 1).

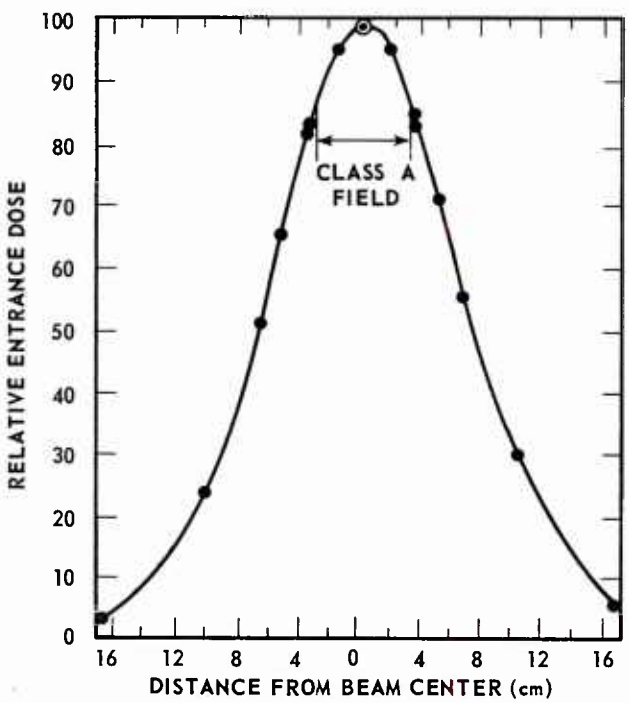

Figure 1. Beam profile at entry into pig head

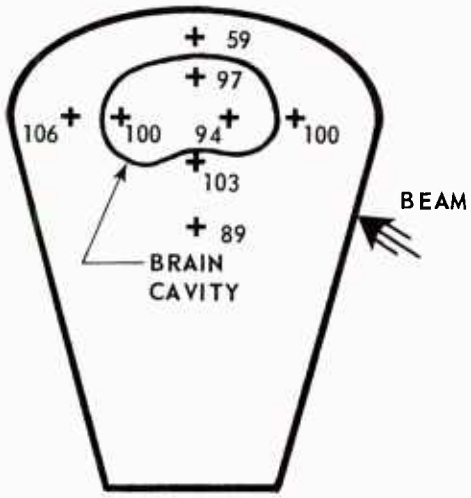

Figure 2. Top view of section of pig-head phantom showing relative doses per 100 rads

Testing. Each postirradiation test period consisted of 10 trials. Pigs that received unfractionated doses were released into the shuttlebox immediately after irradiation. Test periods were initiated in the exposure room at 0, 2.5, 5, 7.5, 10, 15, 20, 25, and 30 minutes after exposure. The animals were then removed from the exposure room and tested again at 45 minutes, 1, 2, 3, and 4 hours postexposure and then every 2 hours for the first 24 to 48 hours after irradiation. Thereafter, they were tested twice daily until they were permanently incapacitated prior to death.

The limited time between the two doses given less than 30 minutes apart did not allow for testing between dose fractions. These animals were not released from the exposure box until after the second dose had been delivered. The pigs that received the doses 30 minutes apart were released and tested for 15 minutes after the first dose. They were then returned to the restraint box. After reirradiation these animals were tested on the same schedule as those receiving unfractionated doses.

The statistical significance of the performance data was tested by one-way analysis of variance and the Student-Newman-Keuls multiple range test. $P \leq 0.01$ was considered statistically significant.

III. RESULTS

Performance. The postirradiation performance (percent avoidance) of individual pigs is given in Table II. The data listed in Table III show that early postirradiation performance of pigs that received head-only irradiation with high energy electrons from the LINAC was not significantly different from that of pigs that received whole-body mixed gamma-neutron irradiation from the reactor.

The effects of the 4400-rad initial dose were, in many cases, still being manifested when the second dose was delivered. Therefore, with short time intervals between doses (3 minutes or less) both doses undoubtedly contributed to some extent to the performance decrement observed after the fractionated doses. By determining the residual injury remaining with time after a single 4400-rad dose for the different fractionation intervals, the specific contributions for each of the two doses to the total performance decrement can be evaluated.

The performance decrement following the initial 4400-rad dose was adjusted to be equivalent to test periods of 15 minutes beginning at either 0.3, 1.6, 3.0, or 30 minutes after irradiation. Omissions (escapes and failures) for these time periods were 37, 32, 29, and 2 percent, respectively (Table IV). These values represent the amount of performance decrement attributed only to the initial dose. The contribution of the first and second doses to total early performance decrement is shown in Figure 3 and given in Table IV. The second dose contributed to performance

Table II. Performance of Miniature Pigs after Two 4400-Rad Doses of Radiation to the Brain

Time between doses (min)	Duration of early performance decrement* (min)		Percent avoidance during first 15 minutes		Duration of satisfactory performance† (days)
	Fraction 1	Fraction 2	Fraction 1	Fraction 2	
$\approx 10^{-4}$	-	20	-	1.7	14
	-	15	-	0	13
	-	45	-	15	13
	-	‡	-	0	‡
	-	45	-	0	0.5
	-	‡	-	0	‡
	-	1440	-	0	6
	-	7.5	-	46.7	10
0.3	-	15	-	10	3
	-	‡	-	0	‡
	-	20	-	1.7	3
	-	25	-	11.7	6
	-	20	-	1.7	6
	-	15	-	48.3	3
	-	240	-	0	<0.5
	-	15	-	3.3	6
1.6	-	5	-	53.3	7
	-	7.5	-	50	7
	-	5	-	70	11
	-	5	-	63.3	5
	-	10	-	18.3	6
	-	15	-	26.7	2
	-	25	-	21.7	6
	-	‡	-	5	‡
3.0	-	7.5	-	65	4
	-	5	-	81.7	2
	-	2.5	-	85	2
	-	2.5	-	80	3
	-	5	-	66.7	11
	-	5	-	46.7	11
	-	5	-	70	5
	-	7.5	-	68.3	3
30.0	2.5	0	90.0	100.0	7
	0	0	100.0	100.0	9
	>15	2.5	6.6	90.0	9
	0	0	96.6	98.8	13
	10	0	30.0	96.6	12
	5	2.5	76.6	90.0	9
	>15	0	10.0	97.7	13
	5	0	81.6	100.0	13

* Proficiency of less than 90 percent avoidance
† Proficiency of 90 percent avoidance
‡ Unsatisfactory performance after irradiation

Table III. Comparison of Performance for the First 15 Minutes after Whole-Body Exposure to Mixed Gamma-Neutron Radiation (TRIGA) and Head-Only Exposure to a High Energy Electron Field (LINAC)

	Percent avoidance ± S. E.*	
	Fractionated dose 4400 rads + 4400 rads	Unfractionated dose 8800 rads
	(60 min apart)	
TRIGA†	50.5 ± 12.2 95.3 ± 1.9	6.7 ± 4.3
	(30 min apart)	
LINAC	61.4 ± 13.9 94.8 ± 2.6	7.9 ± 5.8

* Standard error
† Midbrain dose

Table IV. Miniature Pig Sensitivity to the Second of Two 4400-Rad Doses: Rapid Reduction in Performance Decrement as a Function of Increasing Time Between Doses

Time (t) between doses (min)	Average percent avoidance ± S.E.*	Average percent omission+			Relative sensitivity to second dose
		Total dose $(O_{TD}(t))$	Dose 1 $(O_{D1}(t))$	Dose 2 $(O_{TD}(t) - O_{D1}(t))$	$(O_{TD}(t) - O_{D1}(t)/53.5)$
10^{-4}	7.9 ± 5.8‡	92.1 ± 5.8	38.6 ± 14.1	53.5 ± 15.2	1.000 ± .28
0.3	9.6 ± 5.8‡	90.4 ± 5.8	37.0 ± 13.8	53.4 ± 15.0	0.998 ± .28
1.6	38.5 ± 8.4	61.5 ± 8.4	32.0 ± 13.0	29.5 ± 15.5	0.551 ± .29
3.0	70.4 ± 4.3§	29.6 ± 4.3	29.0 ± 12.1	0.6 ± 12.8	0.011 ± .24
30	94.8 ± 2.6§	5.2 ± 2.6	2.0 ± 1.3	3.2 ± 2.9	0.060 ± .05

* Standard error (eight pigs per group)
+ Escapes and failures considered together
‡ Significantly lower performance ($p < 0.01$)
§ Significantly higher performance ($p < 0.01$)

decrement only when the two doses were given no more than 1.6 minutes apart. At longer time intervals, omissions could be attributed solely to the residual injury from the initial dose.

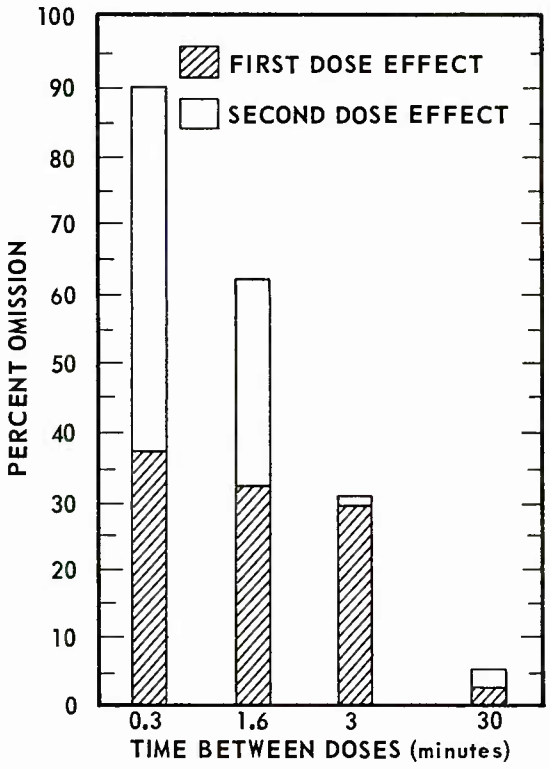

Figure 3. The contribution of the first and second 4400-rad doses to total early performance decrement observed after the second dose fraction

For any time interval (t) between the two dose fractions, the sensitivity of the pigs to the second dose could be calculated from the expression:

$$\text{Relative sensitivity} = \frac{O_{D2}(t)}{O_{D2}(t=0)}$$

where O_{D2} represents percent omission for the second dose fraction. These values, however, were not directly obtainable and were calculated from experimental data using the expanded expression:

$$\text{Relative sensitivity} = \frac{O_{TD}(t) - O_{D1}(t)}{O_{TD}(t=0) - O_{D1}(t=0)}$$

where O_{TD} and O_{D1} represent percent omission for the total dose and for the first dose fraction, respectively. The average performance data (percent avoidance and omission) for the first 15 minutes after the second 4400-rad dose for the various time intervals are given in Table IV and Figure 4. The results of calculations using these data are also given in Table IV.

The values in Table IV (columns 4 and 5) indicate that the animals became markedly insensitive to the second dose soon after the initial dose. When the two doses were given 1.6 minutes apart and although approximately 85 percent (32.0/38.6) of the transient effects from the first dose still remained, avoidance was five times better (38.5/7.9, column 2) than that after an unfractionated dose. This results in a 55 percent (29.5/53.5) decrease in sensitivity to the second dose. When the doses were 3 minutes apart, 75 percent of the transient effects from the first dose was still evident. There was a ninefold improvement in avoidance compared to an unfractionated dose. Thus, the pigs were essentially insensitive to the second dose. By 30 minutes postirradiation, the animals had recovered completely from the temporary effects of the first dose and were completely insensitive to the early transient effects of the second 4400-rad dose.

Clinical symptoms. All pigs that received the unfractionated 8800-rad dose convulsed within seconds after irradiation and became comatose shortly afterwards. As the animals recovered from these effects, they remained very ataxic for many minutes and several animals never performed satisfactorily after irradiation. These neurological symptoms were less severe as the time between dose fractions was increased. When the doses were 3 minutes apart, most pigs experienced only

ataxia; and when the doses were 30 minutes apart, the symptoms were totally lacking after the second dose of radiation.

Survival times are given in Table V. The most notable feature is the incidence of deaths within 1 day postirradiation when the two doses were separated by 0.3 minute or less. Nearly all other pigs survived for 15 to 30 days after irradiation.

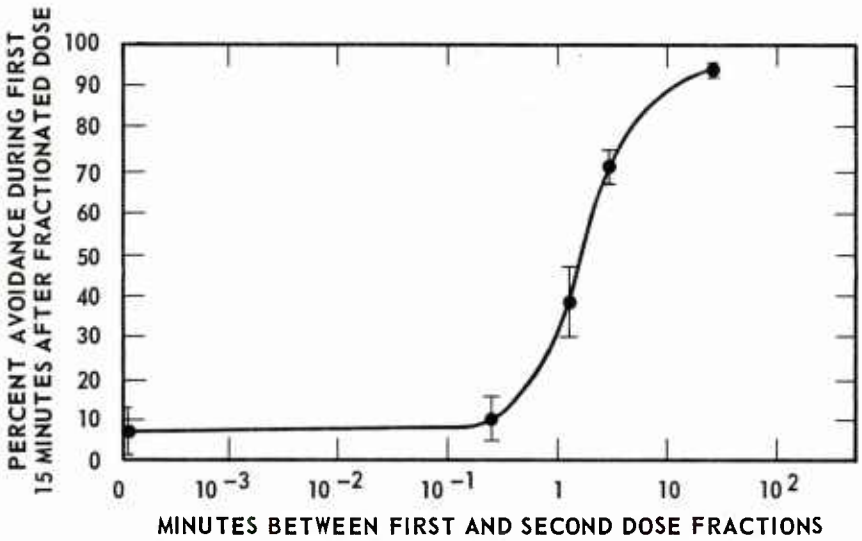

Figure 4. Performance after fractionated doses as a function of time between the two dose fractions

Table V. Survival Time of Miniature Pigs after Two 4400-Rad Doses to the Brain

Survival time (days)	Minutes between doses				
	$\approx 10^{-4}$	0.3	1.6	3	30
≤1	3 (18 h)*	2 (5 h)	0	0	0
>1	5 (21 days)	6 (21 days)	8 (21 days)	8 (20 days)	8 (27 days)

* Number of pigs (median survival time)

IV. DISCUSSION

Since the radiation dose was delivered primarily to brain structures, it is concluded that the increased radioresistance to the second dose fraction was initiated by changes in central nervous system (CNS) function.

Because the increased radioresistance of miniature pigs was both rapid and time dependent, physicochemical processes alone are insufficient to explain our data. Biochemical and possibly physiological processes are also involved. Earlier work[7] showed that the radioresistance could still be observed even though the time interval between supralethal doses was increased to 50 hours. Thus, these processes appear to be irreversible. Further investigations into the mechanism of brain response to supralethal radiation doses should be addressed to defining the site and nature of the primary biochemical lesions and their relationship to known physiological[5] and behavioral effects.[6,7,19]

The maximum possible extent of CNS radioresistance induced by the initial dose was not determined in this study. A similar radioresistance for greater second doses of radiation may exist. It was previously observed that, whether the dose is fractionated or not, performance of irradiated miniature pigs rapidly deteriorated as the total dose approached 13,000 to 14,000 rads.[7] Therefore, with an initial dose of 4400 rads, the maximum second dose for which a reduced CNS response would be observed could be in the vicinity of 8000 rads.

Trained rats[6] and rhesus monkeys[9] also performed much better after the second of two doses given 20 minutes to 24 hours apart. Although shorter time intervals between doses were not examined and although these animals received whole-body

irradiation, the results are consistent with those obtained from pigs in this and earlier studies.[7] This suggests that CNS radioresistance observed after a supralethal dose of radiation is a generalized phenomenon observable not only in these but possibly also in other animal species. Further, not only nervous tissues but also other tissues, in which cells are of the fixed postmitotic type, may become refractory to additional radiation insult after a single high dose. It would be pertinent, therefore, not only to determine the response of other tissues to fractionated supralethal doses of radiation but also to ascertain if similar responses could be induced by stresses other than radiation.

The survival time data in Table V indicate that five of the eight pigs which received unfractionated supralethal doses of high energy electrons to the brain survived significantly longer (ranging from 4 to 21 days) than any of the eight pigs which received unfractionated doses of similar magnitude of mixed gamma-neutron radiation to the entire body (ranging from 0.06 to 3 days).[7] These data suggest that, since whole-body irradiated animals died earlier than head-irradiated animals, effects upon physiological systems other than the brain contributed to their deaths.

Kundel has shown that peripheral vascular damage at doses greater than 3000 R is manifested before loss of fluids and electrolytes can occur from gastrointestinal ulceration and before neurologic lesions are observed.[12] Experiments in dogs[16] and rabbits[10] have shown that head-only irradiation can induce hypotension but that at least a tenfold increase over the required total body dose is needed. These results were verified in a recent study in which a significant decrease in blood pressure occurred in dogs within 8 minutes after about 16,000 rads.[20]

The hypotension occurred only when the trunk was irradiated. After supralethal whole-body doses of gamma-neutron radiation, monkeys became hypotensive within 60 minutes postirradiation.[19] Unfortunately, no head-only irradiations were performed. Furthermore, Fanger and Lushbaugh, in a human case study, concluded that peripheral vascular damage was the primary cause of hypotensive shock and rapid death within 2 days after a total body exposure of 8800 rads of gamma-neutron radiation.[8] Thus, the survival time data obtained in the current study are consistent with previous experimental evidence, in that early death may not be primarily due to CNS effects. The suggestion by Fanger and Lushbaugh[8] that a vascular radiation syndrome should be included as a radiobiologic mode of death distinct from the hematologic, gastrointestinal, and neurologic syndromes is definitely supported by findings in this study.

As mentioned above, a biphasic survival pattern following head-only irradiation was manifested by early deaths within a few hours and by later deaths within several days. However, early deaths occurred only when doses were separated by 10^{-4} to 0.3 minute. When the time interval between doses was increased to 1.6 minutes or more, all animals survived for several days. Animals that died within a few hours after head-only irradiation remained comatose, with death appearing to be the direct result of brain injury. All animals that lived for several days also showed a temporary neurologic syndrome after the first dose, but the injury sustained was insufficient for early death. These animals became refractory to the second dose and ultimately died days later apparently of causes other than primary brain injury. This opinion on the mechanism of death is supported by the reported

absence of well-defined neuropathological changes after supralethal doses of radiation.[5,8] To induce neurologic death, it was suggested that a prompt dose of greater than 10,000 rads must be delivered to the brain.[8]

Edema and ulceration of superficial tissues of the head contributed to a marked decrease in food and water intake beginning about 1 week after irradiation. Thus, these pathological changes contributed indirectly to the pig's death several weeks after irradiation. Similar observations and survival times have been reported for head-only irradiated monkeys.[17]

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R. L. Chaput and P. A. Berardo with the technical assistance of E. L. Barron

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13. ABSTRACT

Clinical symptoms and performance were evaluated after shuttlebox-trained miniature pigs received two 4400-rad doses separated by time intervals of 10^{-4} to 30 minutes. The doses were delivered to the head by 45 MeV electrons from the AFRRI electron linear accelerator (LINAC). There was no significant difference in neurological symptoms (convulsions, coma, ataxia) or in performance after the second dose between animals that received the two doses 10^{-4} or 0.3 minute apart. As the time interval between doses was increased from 0.3 to 3 minutes, however, neurological symptoms declined and performance improved markedly after the second dose. When the doses were 30 minutes apart, the pigs showed no decrease in performance within the initial 30 minutes postirradiation. It was concluded that more than physicochemical processes were involved in the increased radioresistance to the second dose of radiation.

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